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10/549,301	07/17/2006	Jacqueline Dalby-Payne	FBR0002US.NP	2194

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,301	DALBY-PAYNE ET AL.	
	Examiner	Art Unit	
	Jae W. Lee, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-77* is/are pending in the application.

4a) Of the above claim(s) *63-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09/15/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/15/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

In the preliminary amendment of the claims, filed on 09/15/2005, Applicant's cancellation of Claims 1-43 and addition of new Claims 44-77 are acknowledged.

Claims 44-77 are pending in this application.

Priority

A claim of priority to the PCT/AU04/00358, filed on 03/22/2004, and AUSTRALIA 20033901316, filed on 03/21/2003, is acknowledged.

Election

Applicant's election with traverse of Group I, Claims 44-62 and SEQ ID NO: 11 encoded by SEQ ID NO: 7 drawn to TPM 1, is acknowledged. The traversal is on the ground(s) that Davis et al. do not teach the special technical feature that is shared between Groups I and II because Davis et al. teach the untranslated RNA of tropomyosin. Applicants also argue that SEQ ID NO: 11 has about 62% sequence homology to SEQ ID NO: 12, therefore, substantial structural identity does exist between proteins of Group (A)-(D) thereby constituting unity of invention under PCT Rule 13.2.

In response to Applicant's traversal, the Examiner finds Applicants argument persuasive because Davis et al. does not teach the special technical feature shared

between Groups I and II. However, based on the reference of Dunn et al. (Altered tropomyosin expression in essential hypertension, Hypertension, Feb. of 2003, 41: 347-354), the previous restriction requirement is maintained. Dunn et al. teaches methods comprising analyzing expression levels of different Tropomyosin isoforms (see Figure 2 on pg. 350), wherein altered expression levels of tropomyosin indicates that regulations of cell surface protein activity, i.e., sodium-lithium countertransporters (33-kDa extrinsic membrane protein, see pg. 347, left column, 1st paragraph, also see Figures 5 and 6 on pg. 352), which corresponds to the limitation of claim 1, in the recitation of

> "the method comprising analysing an activity or cellular location of tropomyosin, expression levels of tropomyosin, or binding of tropomyosin to one of its binding partners in the presence of a candidate compound, wherein altered tropomyosin activity or cellular location, altered expression levels of tropomyosin or an altered level of binding of tropomyosin to its binding partner in the presence of the compound indicates that the compound regulates the activity of a cell surface protein,"

and thus, the shared technical feature of the groups is not a "special technical feature", unity of invention between the groups does not exist.

Furthermore, Applicants argue that a mere 62% sequence homology between SEQ ID NO: 11 and 12 is a substantial structural identity. However, this argument is not persuasive because these sequences are structurally different proteins by 38% or more in terms of amino acid sequence homology, and where structural identity is required, such as for hybridization or expression, the different sequences have different effects.

This notion of different structures producing different effects is also illustrated in Applicants' specification in paragraph [0094] on pg. 17, hereby quoted for Applicants' convenience: "[t]he various tropomyosin isoforms have different binding affinities for actin and this is thought to result in a differential effect on the stability of actin microfilaments." Therefore, they lack unity of invention under PCT Rule 13.2.

Claims 63-77 and Groups (B) SEQ ID NO: 12 encoded by SEQ ID NO: 8 drawn to TPM 3, (C) TMP5a, (D) TMP5b, are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claims 52, 53, 60 and 61 are objected to because of the following informalities:

Claims 52, 53, 60 and 61 are objected for containing non-elected subject matter, i.e., SEQ ID NO: 12 encoded by SEQ ID NO: 8 drawn to TPM 3, TMP5a and TMP5b.

Claims 48, 52, 58 and 60 are objected to because the recitation of "TPM 1", "CEACAM1" and "S100A2" should be in parenthesis and follow the phrase it abbreviates when used for the first time.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 48, 49, 58 and 59 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 48 and 58 recite phrases, "calponin," "CEACAM1," "endostatin," "Enigma," "Gelsolin," and "S100A2," which are unclear. It is unclear with respect to what is encompassed by those phrases. It is noted by the Examiner that in paragraph [0166] of the specification, Applicants disclose:

> "In a preferred embodiment of the invention the tropomyosin binding partner is selected from the group consisting of calponin (Childs et al. BBA 1121: 41-46, 1992), Cancinoembryonic antigen cell adhesion molecule 1 (CEACAM1) (Schumann et al., J. Biol. Chem. 276 (50):47421-33, 2001), endostatin (MacDonald et al. J. Biol. Chem. 276, 25190-25196, 2001), Enigma (Guy et al. FEBS letters 10: 1973-1984, 1999), Gelsolin (preferably sub-domain 2) Koepf and Burtnick FEBS 309(1): 56-58, 1992), S100A2 (Gimona et al. J. Cell Sci. 110: 611-621, 1997) and actin. In a further preferred embodiment, the tropomyosin binding partner is actin."

However, the disclosure of "a preferred embodiment" followed by mere citations of references fail to clearly define the breadth of each terms as recited above.

Claims 49 and 59 recite the phrase, "sub-domain 2 of Gelsolin," which is unclear. It is unclear with respect to what is encompassed by the "sub-domain 2" of Gelsolin.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-62 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims are directed to a genus of methods of screening for a compound that regulates any activity of a cell surface protein, the method comprising analysing any activity or cellular location of any tropomyosin, expression levels of any tropomyosin, or binding of any tropomyosin to one of its binding partners in the presence of a candidate compound, wherein altered tropomyosin activity or cellular location, altered expression levels of tropomyosin or an altered level of binding of tropomyosin to its binding partner in the presence of the compound indicates that the compound regulates any activity of any cell surface protein.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of [compositions or methods], it must be clear that: (1) the identifying characteristics of the claimed [compositions or methods] have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The specification discloses an exemplary method comprising analyzing localization of tropomyosin containing the amino acid sequence as set forth in SEQ ID NO: 11 encoded by the exon 1b of *TMP 1* gene as set forth in SEQ ID NO: 7 with the cystic fibrosis transmembrane conductance regulator (CFTR). However, this is inadequate written description for a genus of methods of screening for a compound that regulates any activity of a cell surface protein, the method comprising analysing any activity or cellular location of any tropomyosin, expression levels of any tropomyosin, or binding of any tropomyosin to one of its binding partners in the presence of a candidate compound, wherein altered tropomyosin activity or cellular location, altered expression levels of tropomyosin or an altered level of binding of tropomyosin to its binding partner in the presence of the compound indicates that the compound regulates any activity of any cell surface protein.

The specification does not provide a disclosure of any particular structure to function/activity relationship, i.e., any structure of (1) any tropomyosin, (2) any binding partner or (3) any cell surface protein, to any function such as (A) changes in any

tropomyosin activity, (B) changes in any tropomyosin expression or (C) changes in any cell surface protein activity in the claimed genus of methods. The specification also lacks description with respect to what function, if any, is required for any tropomyosin, binding partner and cell surface protein. Further, the specification fails to describe any identification of structural characteristics or properties of any tropomyosin, binding partner and cell surface protein. It is noted by the Examiner that there are as many as 17 different isoforms of tropomyosin according to Dalby-Payne et al. (Polarization of Specific Tropomyosin Isoforms in Gastrointestinal Epithelial Cells and Their Impact on CFTR at the Apical Surface, Molecular Biology of the Cell, Vol. 14, 4365–4375, November 2003), all of which are structurally divergent (see pg. 4368, Figure 1). It is also noted by the Examiner that many of them lack the exon 1b of *TMP 1* gene.

Given the lack of additional representatives of a genus of methods of screening for a compound that regulates any activity of a cell surface protein, the method comprising analysing any activity or cellular location of any tropomyosin, expression levels of any tropomyosin, or binding of any tropomyosin to one of its binding partners in the presence of a candidate compound, wherein altered tropomyosin activity or cellular location, altered expression levels of tropomyosin or an altered level of binding of tropomyosin to its binding partner in the presence of the compound indicates that the compound regulates any activity of any cell surface protein as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 44-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for SEQ ID NO: 11 encoded by the exon 1b of *TMP 1* gene as set forth in SEQ ID NO: 7, does not reasonably provide enablement for any method of screening for a compound that regulates any activity of a cell surface protein, the method comprising analysing any activity or cellular location of any tropomyosin, expression levels of any tropomyosin, or binding of any tropomyosin to one of its binding partners in the presence of a candidate compound, wherein altered tropomyosin activity or cellular location, altered expression levels of tropomyosin or an altered level of binding of tropomyosin to its binding partner in the presence of the compound indicates that the compound regulates any activity of any cell surface protein. Therefore, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Claims 44-62 are so broad as to encompass any of method of screening for a compound that regulates any activity of a cell surface protein, the method comprising analysing any activity or cellular location of any tropomyosin, expression levels of any tropomyosin, or binding of any tropomyosin to one of its binding partners in the presence of a candidate compound, wherein altered tropomyosin activity or cellular location, altered expression levels of tropomyosin or an altered level of binding of tropomyosin to its binding partner in the presence of the compound indicates that the compound regulates any activity of any cell surface protein.

The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the "tropomyosin," "binding partner," and "cell surface

protein." Since the amino acid sequence of a peptide determines its structural and functional properties, predictability of which peptides can be used while obtaining the desired function requires a knowledge of and guidance with regard to which amino acids in the peptide's sequence, if any, are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the peptide's structure relates to its desired function. In addition, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of different peptides/proteins.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any tropomyosin, any binding partner, any cell surface protein used in the claimed methods because the specification does not establish: (A) regions of the protein structure which may be modified without affecting desired activities of any tropomyosin, any binding partner, any cell surface protein, i.e. actin binding activity; (B) the general tolerance of any tropomyosin, any binding partner,

any cell surface protein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any tropomyosin, any binding partner, any cell surface protein with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Because of this lack of guidance, and the fact that the relationship between the polypeptide sequence of a protein and its activity/function is not well understood and unpredictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to make and use the claimed methods.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any tropomyosin, any binding partner, any cell surface protein to be used in the claimed screening method, having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 44-62 are rejected under 35 U.S.C. § 102(b) as being anticipated by Watkins et al. (Abnormal thiol reactivity of tropomyosin in essential hypertension and its association with abnormal sodium-lithium countertransport kinetics, Journal of Hypertension 2001, 19: 485-493) in view of evidentiary references, Dunn et al. (Altered Tropomyosin Expression in Essential Hypertension, Hypertension, Feb. of 2003, 41: 347-354), and Sigma catalog (Biotin-maleimide, see attached).

The instant claims are drawn to a method of screening for a compound that regulates an activity of a cell surface protein, the method comprising analysing an activity or cellular location of tropomyosin, expression levels of tropomyosin, or binding of tropomyosin to one of its binding partners in the presence of a candidate compound, wherein altered tropomyosin activity or cellular location, altered expression levels of tropomyosin or an altered level of binding of tropomyosin to its binding partner in the presence of the compound indicates that the compound regulates the activity of a cell surface protein.

Watkins et al. teach that abnormal thiol reactivity of tropomyosin in essential hypertension is associated with abnormal sodium-lithium countertransport kinetics. Watkins et al. specifically teach a method comprising analyzing binding of tropomyosin to one of its binding partners, i.e., Biotin-maleimide, which is a thiol-specific biotinylation agent (see attached Sigma catalog for Biotin-maleimide), in the presence of a candidate

compound, i.e., N-ethylmaleimide (NEM), wherein altered level of binding of tropomyosin to Biotin-maleimide in the presence of the NEM indicates that the compound increases the activity of a cell surface protein, i.e., sodium-lithium countertransporter activity is increased (see Table 1 on pg. 491, wherein Vmax and Km are increased in the presence of NEM in Essential hypertensive compared to Untreated; pg. 486 under "Alkylation and biotin labeling of thiol groups"; pg. 489 under "Abnormal NEM reaction with tropomyosin in EHT"; pg. 489 under "Abnormal Na/Li CT kinetics are related to thiol modification of tropomyosin; Figures 1-4; and Tables 1 and 2).

Claims 48, 49, 58 and 59 are included under this rejection because the claimed methods are drawn to "analyzing an activity of tropomyosin," which do not require calponin, CEACAM1, endostatin, Enigma, Gelsolin or S100A2.

Claims 52 and 60 are included under this rejection because in the evidentiary reference of Dunn et al., the authors specifically point out that the tropomyosin they have previously characterized in Watkins et al. is encoded by the human gene *TPM 1* containing exon 1b (see pg. 351, Figure 3), which reads on Applicant's SEQ ID NO: 11 (exon 1b of human *TPM 1* gene). Also, Dunn et al. refer to the reference of Watkins et al. by citing that "[w]e have previously shown the sensitivity of Na^+/Li^+ CT [sodium-lithium countertransporter] to tropomyosin influences on the cytoskeleton by the change in Na^+/Li^+ CT kinetics with liposome-delivered tropomyosin antibodies" (see pg. 353, left column, lines11-15).

Claims 54 and 57 are included under this rejection because they are drawn to methods comprising identical active steps as recited in Claim 44. The main difference

between Claim 44 and Claims 54 and 57 lies in the "use" of the compound in the treatment of cystic fibrosis, and such "uses" do not further limit the breadth of Claimed methods as recited in Claims 54 and 57.

Claim 62 is included under this rejection because formulating a compound, NEM (30 mmol/l in choline medium B), is taught by Watkins et al. (see pg. 486, left column, 1st paragraph under "Alkylation and biotin labeling of thiol groups").

Therefore, Watkins et al. anticipate the Applicants' claimed method of screening for a compound that regulates an activity of a cell surface protein, the method comprising analysing an activity or cellular location of tropomyosin, expression levels of tropomyosin, or binding of tropomyosin to one of its binding partners in the presence of a candidate compound, wherein altered tropomyosin activity or cellular location, altered expression levels of tropomyosin or an altered level of binding of tropomyosin to its binding partner in the presence of the compound indicates that the compound regulates the activity of a cell surface protein.

Conclusion

Claims 44-62 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen K. Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER